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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/556,937	10/31/2006	Michael R. Costa	EX04-044C-US	6980
63572 7590 01/31/2011 MCDONNELL BOEHNEN HULBERT @ BERGHOFF LLP 300 SOUTH WACKER DRIVE SUITE 3100 CHICAGO, IL 60606				
EXAMINER GEBREYESUS, KAGNEW H				
ART UNIT 1656		PAPER NUMBER		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/556,937

Applicant(s)

COSTA ET AL.

Examiner

KAGNEW H. GEBREYESUS

Art Unit

1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 November 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 8-12, 17-19 and 26-28, 30 is/are pending in the application.
- 4a) Of the above claim(s) 2-7, 13-15, 20-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 8-12, 17-19, 26-28 and 30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-946)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB-08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No.(s)/Mail Date: _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Applicant's response on 11/24/2010 to the Office Action mailed on August 24, 2010 is acknowledged. Claims 1-15, 17-28 and 30 are currently pending in this application. Claims 1, 8, 11, 12, 17, 18 and 26 have been amended. Claims 1, 8-12, 17-19 and 26-28, 30 are present for examination. Claims 2-7, 13-15, 20-25 remain withdrawn from consideration.

All objections and rejections not reiterated from the previous Office Action are hereby withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8-9, 11-12, 17-19, 26-28 were rejected under 35 U.S.C. 102(b) as being anticipated by US 2002/0025931 A1 (Meyers et al).

The method steps in claim 1, 8-9, 11-12, 17-19, 26-28-claim 29 is cancelled-- are drawn to an assay system that uses the polynucleotide sequence of SEQ ID NO: 5 (encodes SNF1LK) or any functional fragment that encodes a polypeptide that comprises residue 27-278 of SEQ ID NO: 5 in the presence of a candidate test agent

that modulates SNF1LK and determining the effect of the candidate test agent on the activity of the SNF1LK.

In the above assay system, any agent that has an effect on the activity of the SNF1LK can be considered a candidate PTEN pathway modulating agent. Furthermore claims 1- and dependent claims thereof encompass a second assay system comprising a cell culture or non-human animals which express any MARK (see page 5, line 5-14 of the specification teaches that "MARK" encompasses a genus of kinases including the SNF1LK of SEQ ID NO: 5) in the presence of a test agent and detecting a test agent biased activity.

It should be noted that since SNF1LK is implicitly part of the PTEN pathway it can be broadly interpreted that any aberrance in SNF1LK would result in aberrance in PTEN pathway -- thus a defective PTEN function.

Applicants argue that a claim is anticipated under 102(b) if each and every element as set forth in the claim is found in a single art reference and that no difference may exist and must contain an enabling disclosure and must be so precise and so particular that any person skilled in the art can construct and operate it without further experiments and without further exercise of inventive skill...

Applicants further state that Meyer et al. does not teach each and every step of the presently claimed methods and therefore fails to anticipate the instant invention. Applicants argue that while Meyer et al. teach certain polypeptide sequences having kinase activity and sequence homology to SNF1LK ("clone 3714"), polynucleotides encoding the polypeptides, and methods for modulating the expression or activity of the

polypeptides, Meyer et al make no mention whatsoever of the PTEN pathway or any association between clone 3714 sequences and the PTEN pathway. Thus, Meyer et al. fails to even recognize that clone 3714 (i.e., SNF1LK) is involved in the PTEN pathway. Accordingly, Meyer et al. fails to teach a method for identifying a candidate PTEN pathway modulating agent using two separate assay systems that (1) detect the expression of SEQ ID NO: 5 and (2) measure a change in the PTEN pathway. Furthermore Applicant's argue that they were the first ones to determine that SNF1LK's involvement in the PTEN pathway

Applicant's argument has been carefully considered however the argument is not found persuasive.

Meyers et al teach a screening method for identifying a compound that binds to or modulates the activity of a protein encoded by SEQ ID NO: 1 comprising;

- providing an indicator composition comprising an activity of a SEQ ID NO: 1 encoded protein with kinase activity);
- providing a test compound, and determining the effect of the test compound on activity protein encoded by SEQ ID NO: 1.

In addition, paragraph [0298] - [0301] Meyer et al teach a screening assays that encompasses a method for identifying modulators (i. e., candidate or test compounds or agents) which have a stimulatory or inhibitory effect on, for example, the expression or activity of SNF1LK encoded by SEQ ID NO: 1.

It should be noted that since SNF1LK is part of the PTEN pathway, it would implicitly mean that any aberrance in SNF1LK would result in aberrance in PTEN

pathway (thus a defective PTEN pathway function). Furthermore any agent that has an effect on SNF1LK is considered a candidate PTEN pathway modulating agent because these proteins are in the same pathway. In addition claim 1(d) of the instant application encompasses determining the difference in expression level of SEQ ID NO: 5 (SNF1LK) in the presence or absence of a test agent to identify a PTEN pathway modulating agent (thus reaffirms that SNF1LK and PTEN are part of the same pathway). Therefore Applicant's argument stating that Meyer et al. fails to teach a method for identifying a candidate PTEN pathway modulating agent is not found persuasive since a PTEN pathway modulating agent is defined by the effect of the agent on SNF1LK expression levels.

With regards to measuring a change in the PTEN pathway, no specific steps are recited other than a general cell based assay. Paragraph [0220] of Meyers et al teaches that in a preferred embodiment, a mutant SNF1LK (clone "3714" or SEQ ID NO: 3) can be assayed for the ability to: 1) regulate transmission of signals from cellular receptors, e.g., cardiac cell growth factor receptors; 2) control entry of cells into mitosis; 3) modulate cellular differentiation; 4) modulate cell death; or 5) regulate cytoskeleton function, e.g., actin bundling which can all be considered in the PTEN pathway. Thus Applicant's argument is not found persuasive.

Furthermore in a preferred embodiment in paragraph [0308], Meyers et al teach that how to determine the ability of the SNF1LK protein to bind to or interact with a SNF1LK target molecule by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of

a cellular second messenger of the target (e.g., intracellular Ca^{2+} , diacylglycerol, IP_3 , etc.), detecting catalytic/enzymatic activity of the target on an appropriate substrate, detecting the induction of a reporter gene (comprising a target-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, e.g., chloramphenicol acetyl transferase), or detecting a target-regulated cellular response. Thus absent evidence to the contrary, this cell based assay broadly encompasses the second assay system in independent claim 1.

Furthermore Applicants neither present the nexus between SNF1LK and PTEN in a PTEN pathway in a manner that distinguishes the presently claimed method from the method disclosed by Meyers et al nor present any other means of identifying a "PTEN pathway modulating agent" in the specification. Regardless of the link between SNF1LK and the PTEN pathway, Meyer et al's disclosure for example in paragraph [0308] is within the limitation of the second assay recited in the claims absent any evidence to the contrary.

Applicants further argue:

"...In cases where the preamble sets forth the objective of the method and the body of the claim directs that the method be performed to obtain that objective, the courts have found that the preamble gives meaning to the claim. *Jansen v. Rexall Sundown Inc.*, 68 USPQ2d 1154 (Fed. Cir. 2003); *Rapoport v. Dement*, 254 F.3d 1053 (Fed. Cir. 2001). In addition, when the preamble recites additional structure or steps underscored as important by the specification, the preamble may operate as a claim limitation. *Coming Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1257 (Fed. Cir. 1989). In this case, the claims' recitation of a "method of identifying a candidate PTEN pathway modulating agent" gives life and meaning to the preambles' statement of purpose. The preamble is therefore not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of the intentional purpose for which the method must be performed. See *Jansen v. Rexall Sundown Inc.*, 68 USPQ2d 1154..."

Applicant's argument is carefully considered. However in the instant case even assuming that the preamble: a method of identifying a candidate PTEN pathway modulating agent" gives life and meaning to the preambles' statement of purpose, the candidate PTEN pathway modulating agent is determined by measuring the expression levels of a different protein i.e. SNF1LK of SEQ ID NO: 5 in the presence of the test agent. The first step of the assay requires "screening agents for their effect on the expression of SNF1LK which is presumably in the PTEN pathway. Meyer et al second assay encompasses determining the ability of the SNF1LK protein to bind to or interact with an SNF1LK target molecule. The assay is accomplished by determining the activity of the SNF1LK target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (e.g., intracellular Ca^{2+} , diacylglycerol, IP_3 , etc.), detecting catalytic/enzymatic activity of the target an appropriate substrate, detecting the induction of a reporter gene etc.

Furthermore Applicants argue: "... that the teaching of the possible use of toxicity assays does not amount to a teaching of using a second assay system to measure a change in the PTEN pathway, much less amount to an enabling disclosure or a detailed description of such an assay system. Given the failure of Meyer et al. to mention the PTEN pathway or recognize an association between SNF1LK and the PTEN pathway, it certainly fails to provide an enabling disclosure for the use of a first assay system to detect the expression of SEQ ID NO: 5 and a second assay system to measure a change in the PTEN pathway. ..."

Applicant's argument has been carefully considered but not found persuasive because use of a toxicity assay is not the only teaching discussed in Myeres et al.

In paragraph [0220] Meyers et al teach that mutant polypeptide of the invention can be assayed for the ability to: 1) regulate transmission of signals from

cellular receptors, e.g., cardiac cell growth factor receptors; 2) control entry of cells into mitosis; 3) modulate cellular differentiation; 4) modulate cell death (thus apoptosis); or 5) regulate cytoskeleton function, e.g., actin bundling. In addition the activity of the SNF1LK target molecules can be determined by detecting induction of a cellular second messenger of the target (e.g., intracellular Ca^{2+} , diacylglycerol, IP_3 , etc.), detecting catalytic/enzymatic activity of the target an appropriate substrate, detecting the induction of a reporter gene etc. Thus the second assay can encompass the above assays not just a toxicity assay.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 10 was rejected under 35 U.S.C. 103(a) as being unpatentable over Meyers et al in view of Summerton et al (Morpholino antisense oligomers: the case for an RNase H-independent structural type (Biochimica et Biophysica Acta 1489 (1999) 141-158) or Stein et al (A Specificity Comparison of four antisense types: Morpholino, 2'-OMethyl RNA, DNA, and Phosphorothioate DNA. Antisense & Nucleic acid Drug Development 7:151-157 (1997). Claim 10 in the instant application teaches that the nucleic acid modulator is a phosphothioate morpholino oligomer (PMO). Claim 30 in the

instant application is drawn to a nucleic acid modulator wherein said modulator is a dsRNA or an siRNA modulator.

Meyers teaching is discussed above. While Meyers et al teach antisense nucleic acid molecules to modulate transcription, they do not specifically teach siRNA or dsRNA to modulate transcription.

However at the time of the instant invention, the art was mature with regard to the use of siRNA to modulate expression of undesired genes. For example Martinez et al teach siRNAs can be used to suppress expression of point-mutated genes and state that such siRNA can provide the basis for selective and personalized anti-tumor therapy. They further teach that siRNAs have been used for various purposes and have been shown to discriminate between point mutant mRNA targets. Thus given the isolated polynucleotide sequence of SEQ ID NO: 1 (which is considered a functional variant of SEQ ID NO: 5) and the disclosure of a method of suppressing the expression of point-mutated genes it would have been obvious to specifically design an siRNA molecules to modulate/suppress expression of a polypeptide encoded by the same. One of ordinary skill in the art would be motivated to use siRNA in circumstances where it is desirable to suppress expression of aberrant forms of the polynucleotide/polypeptide of the invention. One of ordinary skill would have a reasonable expectation of success because there is no technical impediment that prevents the use of siRNA can be foreseen by a person of ordinary skill in the art.

Accordingly, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

Applicants argue that, the teachings of Meyer, Summerton and Stein, alone or in combination, do not render obvious the present invention because the Office did not demonstrate that the references teach or suggest all the limitations of the claims.

Applicants argue that Meyer et al. fails to teach steps (d) - (f) of the claimed methods. Further, neither Summerton nor Stein cure the deficiencies of Meyer et al because neither Summerton nor Stein are concerned with SNF1LK or the PTEN pathway and therefore offer no teaching whatsoever in this regard.

Applicant's arguments have been carefully considered but not found persuasive. It is the combination of references that has to be considered not just a single reference separately. Thus in response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It is important to note that regardless of the stated purpose in the preamble, the first assay measures the effect of an agent on SNF1LK. This effect on SNF1LK is what is evaluated in the method of identifying an agent that modulates the PTEN pathway. Furthermore no other gene/protein is required in the design of this first assay. Thus the

method of identifying a PTEN pathway modulating agent through the effect of the agent on the expression level of the SNF1LK or a functional fragment thereof is within the limitation of the teachings of Meyer et al. As explained above various cell based assays are considered as the second assay.

Applicants argue: "... Summerton and Stein fail to supplement the teachings of Meyer et al. so as to arrive at the presently claimed methods of identifying a candidate PTEN modulating agent employing the steps of (a) - (f) thus fail to render the instant invention obvious... Furthermore, one skilled in the art would not have been motivated to modify the combined teachings of Meyer, Summerton and Stein to arrive at the presently claimed methods...The combination of references recognize any association between SNF1LK and PTEN pathway and that there is no suggestion or reasonable expectation of success that the SNF1LK polynucleotide can be used in an assay to identify a PTEN pathway modulating agent.

Applicant's argument has been carefully considered however not found persuasive. Summerton et al teach the advantages of using RNase H-independent morpholino antisense oligos (PMO) over RNase H-competent phosphorothioates (S-DNAs). Summerton et al teach that in cell-free and cultured-cell systems where one wishes to block the translation of a messenger RNA coding for a normal protein, RNase H-independent morpholino antisense oligos provide complete resistance to nucleases, generally good targeting predictability, generally high in-cell efficacy, excellent sequence specificity. They teach that significant limitations, including: degradation by nucleases, poor in-cell targeting predictability, low sequence specificity, and a variety of non-antisense activities are seen when using RNase H-competent phosphorothioates (S-DNAs. Thus it would have been obvious to use PMO over other nucleic acid based modulators.

Furthermore Stein et al teach a comparison of efficiency and specificity of four antisense types: Morpholino, 2'-OMethyl RNA, DNA, and Phosphorothioate DNA and state that Morpholino and 2'-OMethyl RNA have superior efficiency and specificity compared to the RNase H dependent antisense nucleic acids (DNA, and Phosphorothioate DNA). Therefore it would have been obvious to use RNase H-independent antisense such as PMOs to avoid the drawbacks discussed by Summerton et al. Furthermore one of ordinary skill in the art would be motivated to use any RNase H-independent antisense such as PMOs because compared to RNase dependent antisense oligos, PMOs have been shown to have higher efficiency and specificity (see Stein et al). One of ordinary skill in the art would have a reasonable expectation of success because the art clearly teaches that RNase dependent oligos and RNase independent oligos such as PMOs are known to be interchangeably used.

Furthermore claim 8, 9 and 30 (not claim 10 as correctly pointed out) were was rejected under 35 U.S.C. 103(a) as being unpatentable over Meyers et al in view of Martinez et al. (Synthetic small inhibiting RNAs: Efficient tools to inactivate oncogenic mutations and restore p53 pathways PNAS vol. 99 no. 23 pages 14849-14854 Oct. 28, 2002). (It should be noted that claim 30 depends on claim 8 and that claim 9 recites an antisense oligomer).

Applicants argue that Martinez fails to cure the deficiencies of the teachings of Myeres et al. Applicants correctly point out that the rejection was not directed to claim 10 and that the rejection is directed to claim 30. The rejection is directed to dependent

claim 30 and claims 8 and 9 that essentially recite a nucleic acid modulator and an antisense oligomer which broadly encompass siRNA.

As discussed previously it is the combination of references that must be considered not just a single reference separately. With regards to Martinez et al it highlights the fact that the art was mature with regard to the use of siRNA to modulate expression of undesired genes. Martinez et al teach siRNAs can be used to suppress expression of point-mutated genes and state that such siRNA can provide the basis for selective and personalized anti-tumor therapy. They further teach that siRNAs have been used for various purposes and have been shown to discriminate between point mutant mRNA targets. Thus given the isolated polynucleotide sequence of SEQ ID NO: 1 (which is considered a functional variant of SEQ ID NO: 5) and the disclosure of a method of suppressing the expression of point-mutated genes it would have been obvious to specifically design an siRNA molecules against the expression of SEQ ID NO: 5 to modulate/suppress the expression of the polypeptide.

Conclusion: No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAGNEW H. GEBREYESUS whose telephone number is (571)272-2937. The examiner can normally be reached on 8:30am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MANJUNATH RAO can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kagnew H Gebreyesus/

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Acting Examiner of Art Unit 1656

January 20, 2011.

/Manjunath N. Rao /

Supervisory Patent Examiner, Art Unit 1656